ORGANIC LETTERS

2011
Vol. 13, No. 2
180−183

Direct Synthesis of *anti*-1,3-Diols through Nonclassical Reaction of Aryl Grignard Reagents with Isopropenyl Acetate

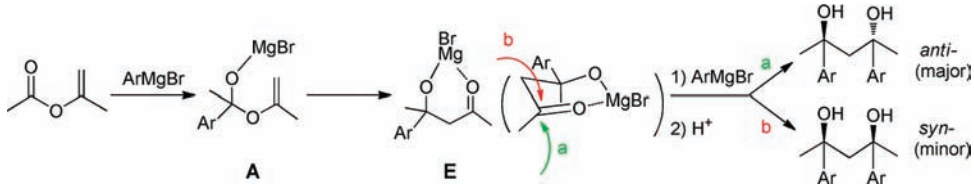
Yinchun Jiao,[†,‡] Chenzhong Cao,[*,‡] and Zaichun Zhou[‡]

School of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, Xiangtan 411201, China, Key Laboratory of Theoretical Chemistry and Molecular Simulation of Ministry of Education, Hunan University of Science and Technology, China, and Hunan Provincial University Key Laboratory of QSAR/QSPR, China

czcao@hnust.edu.cn

Received October 18, 2010

ABSTRACT



A series of symmetrical aromatic 1,3-diols were efficiently synthesized from substituted aryl Grignard reagents and isopropenyl acetate in a one-step reaction that formed *anti* products as the major species. Both experimental and theoretical studies suggested that the reaction involves the formation of a relatively stable intermediate E containing a six-membered ring from intermediate A. The stereoselectivity of the reactions and the molecular structure of the products were confirmed by NMR spectroscopy, X-ray diffraction, and gas chromatography.

The 1,3-diol moiety is present in a number of natural products including polyene macrolide antibiotics, and has some biological activity.[1] A number of conventional methods for the preparation of 1,3-diols have been developed, including: (1) reduction of β-diketones or β-hydroxy ketones,[2,3] (2) reduction of α-hydroxy epoxides,[4] (3) radical-mediated C−H functionalization,[5] (4) highly selective reduction of acyclic β-alkoxy ketones,[6] and (5) silylmethyl radical cyclization of allylic alcohols.[7] Symmetrical and asymmetrical 1,3-diols can be obtained through the first two methods and last three methods, respectively. Numerous diastereoselective reduc-

[†] Central South University and School of Chemistry and Chemical Engineering, Hunan University of Science and Technology.

[‡] Key Laboratory of Theoretical Chemistry and Molecular Simulation of Ministry of Education, Hunan University of Science and Technology, and Hunan Provincial University Key Laboratory of QSAR/QSPR.

(1) (a) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (c) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664.

(2) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019. (b) Barluenga, J.; Resa, J. G.; Olano, B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425. (c) Michel, J.; Canonne, P. *Can. J. Chem.* **1971**, *49*, 4084. (d) Tang, W. J.; Zhang, X. M. *Chem. Rev.* **2003**, *103*, 3029.

(3) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (b) Sarko, C. R.; Collibee, S. E. *J. Org. Chem.* **1996**, *61*, 868. (c) BouzBouz, S.; Janine, C. *Org. Lett.* **2000**, *2*, 501. (d) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403. (e) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A., II *Org. Lett.* **2004**, *6*, 2685. (f) Davis, T. A.; Chopade, P. R.; Hilmersson, G.; Flowers, R. A., II *Org. Lett.* **2005**, *7*, 119. (g) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.

(4) (a) Murai, T.; Kato, S.; Murai, S. *J. Am. Chem. Soc.* **1984**, *106*, 6093. (b) Nilewski, C.; Geisser, R. W.; Ebert, M. O.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 15866. (c) Tu, Y. Q.; Sun, L. D.; Wang, P. Z. *J. Org. Chem.* **1999**, *64*, 629.

(5) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247.

(6) Cullen, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 3143.

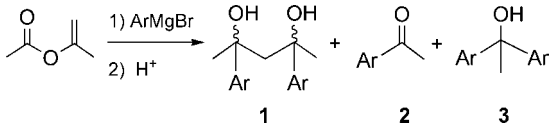
(7) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.

10.1021/ol102520y
Published on Web 12/10/2010

tions of β-hydroxy ketones to form *syn*- and *anti*-1,3-diols have been reported.[8] These procedures suffer from some drawbacks: indispensable catalyst, such as silicone, organolithium, cobalt carbonyl,[9] and silver carbonate, multistep reactions, harsh anhydrous and oxygen-free conditions, and asymmetric aliphatic 1,3-diols as the major product.

Grignard reagents have been widely used by chemists because of their classical synthetic potential via addition to carbonyl derivatives. In this work, a novel protocol to yield symmetrical 1,3-diols through a nonclassical one-step reaction of an aryl Grignard reagent with isopropenyl acetate (Scheme 1) was unintentionally found.

Scheme 1. The Addition of Grignard Reagents to Isopropenyl Acetate



Air-assisted addition of Grignard reagents to olefins generated alcohols with longer carbon chains.[10] It was our intention to investigate what products are obtained if both a C=C double bond and a carbonyl group coexist in a molecule. As such, isopropenyl acetate was selected for reaction with the Grignard reagent phenyl magnesium bromide under dry air. The main product of this reaction was not the expected product but was instead 2,4-diphenylpentane-2,4-diol **1** (Ar = Ph, 85%, Scheme 1), as well as two byproducts **2** and **3** (both with a yield of less than 10%). Further measurements revealed that compound **1** possesses two configurations. The structures of the two isomers (*anti* and *syn*) were unambiguously confirmed by X-ray crystallography (Figure 1), and gas chromatography (GC) showed that the ratio of *anti*:*syn* isomers is up to 6.0:1.0. In ^{1}H NMR spectra of **1**, the methylene protons of *syn*-**1a** occur as an AB-type quartet, whereas those of the *anti*-diol appear as a singlet. In *syn*-**1a**, these two protons should be in different environments and split one another, while those in *anti*-**1a** are in the same environment. Similar results were obtained when this reaction was performed under N_2 protection.

Generally, Grignard reagents react with esters to produce tertiary alcohols through two addition steps. However, the major product in this work is an *anti*-1,3-diol, which is unexpected for the reaction of a Grignard reagent with isopropenyl acetate.

(8) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron.* **1984**, *40*, 2233. (b) Chen, K. M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155. (c) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190. (d) Sarko, C. R.; Collibee, S. E.; Knorr, A. L.; DiMare, M. *J. Org. Chem.* **1996**, *61*, 868. (e) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447. (f) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172. (g) Bartoli, G.; Bellucci, M. C.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Chem.—Eur. J.* **2000**, *6*, 2590.

(9) Murai, T.; Kato, S.; Murai, S. *J. Am. Chem. Soc.* **1984**, *106*, 6093.

(10) Nobe, Y.; Arayama, K.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 18006.

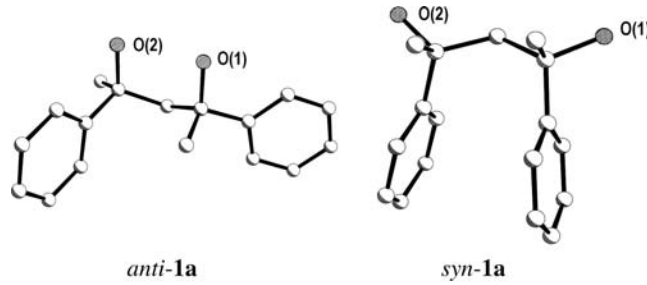
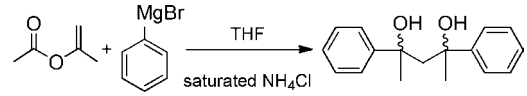


Figure 1. X-ray crystal structures of *anti*-**1a** and *syn*-**1a** (**1** is 2,4-diphenylpentane-2,4-diol).

The results from temperature-controlled experiments agree with our initial result (Table 1). Addition of isopropenyl acetate to a Grignard reagent is exothermic, which indicates that such reactions are accomplished instantly. As shown in Table 1, the yield of 1,3-diol decreases slightly as the reaction temperature is increased. This type of reaction was not sensitive to the reaction temperature (entries 2−5) except for entry 1 at 0 °C and entry 6 under reflux; the yields of product are 42% and 71% while the ratio of the *syn*/*anti* diastereomers were lower to 2.8:1.0 and 3.6:1.0, respectively. The reason for this may be that the reaction is slow at low temperature and the polymerization of isopropenyl acetate would increase with high temperature, which in turn reduces the reaction yield.

Table 1. The Influence of Temperature on the Reaction of Phenyl Magnesium Bromide with Isopropenyl Acetate[a]



1a

entry	temp/°C	*t*/h	*anti*:*syn*[b]	yield (%)[b]
1	0	8	2.8:1.0	42
2	20	6	6.3:1.0	81
3	30	6	6.2:1.0	85
4	40	6	6.2:1.0	80
5	60	6	6.2:1.0	79
6	reflux	6	3.6:1.0	71

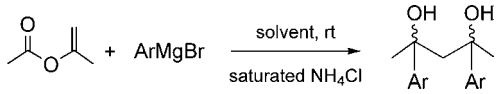
[a] All reactions were carried out with isopropenyl acetate to PhMgBr at a molar ratio of 1.0:2.1; solvent: THF. [b] Products were determined by GC.

Encouraged by this initial result, the reaction conditions, including the reaction time, temperature, ratio of reagents and dry air or N_2 protection, were optimized. The results from these experiments showed that the yield of **1a** can be increased up to 85% (entry 3 in Table 1) when the ratio of isopropenyl acetate to phenyl magnesium bromide is 1.0:2.1 under protection with dry N_2 or air at 30 °C.

The electronic effect of substituents in the aryl Grignard reagents on the reaction was also investigated. Under the optimized reaction conditions, a variety of aryl Grignard

reagents were used in an ambitious one-step protocol for the synthesis of 1,3-diols (Table 2).[11] The results indicated that

Table 2. *Syn*/*Anti* Ratio and Yield of Products in the Reaction of Isopropenyl Acetate with Various Grignard Reagents at Room Temperature



1

entry	Ar	*anti*:*syn*	yield/%
1	Ph	6.0:1.0	85 (**1a**)
2	*p*-MeC_6H_4	6.1:1.0	57 (**1b**)
3	*p*-EtC_6H_4	6.8:1.0	50 (**1c**)
4	*p*-*i*-PrC_6H_4	3.2:1.0	46 (**1d**)
5	*p*-$OMeC_6H_4$	1.5:1.0	35 (**1e**)
6	*p*-$SMeC_6H_4$	100:0[a]	20 (**1f**)
7	*p*-$SiMe_3C_6H_4$	4.6:1.0	21 (**1g**)
8	*p*-$NMe_2C_6H_4$	ND[b]	ND[b]
9	*p*-FC_6H_4	4.7:1.0	45 (**1i**)
10	*p*-ClC_6H_4	9.2:1.0	62 (**1j**)
11	*p*-BrC_6H_4	7.2:1.0	25 (**1k**)
12	*p*-$CF_3C_6H_4$	17.3:1.0	41 (**1*l***)
13	*m*-MeC_6H_4	1.4:1.0	35 (**1m**)
14	*m*-$OMeC_6H_4$	2.5:1.0	37 (**1n**)
15	*m*-FC_6H_4	7.7:1.0	72 (**1o**)
16	*m*-ClC_6H_4	8.8:1.0	66 (**1p**)
17	*m*-$CF_3C_6H_4$	6.1:1.0	73 (**1q**)

[a] The *syn* isomer was not detected by GC; NMR spectrum displayed the *anti* isomer. [b] Not detected.

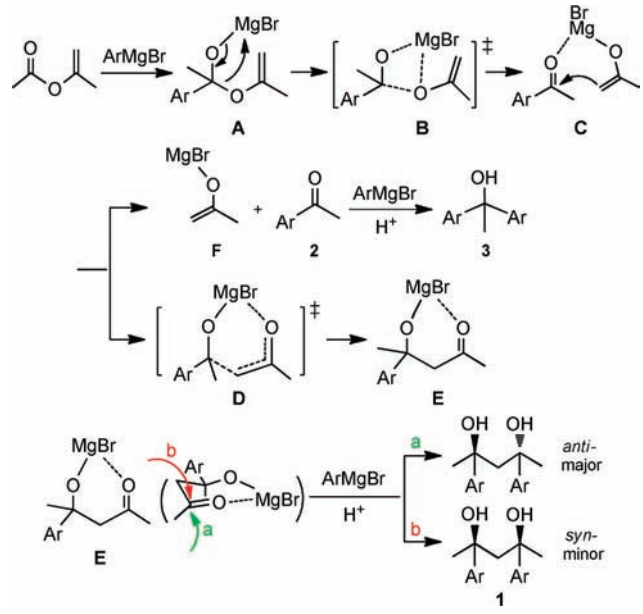
aromatic Grignard reagents bearing either electron-withdrawing or -donating groups such as chloro, fluoro, bromo, methyl, or methoxy substituents are suitable for the reaction. A total of 16 1,3-diols were obtained, and some isomers were separated. The stereochemical assignment of these compounds was determined from their analogy with compound **1a**, for which conclusive X-ray data were available and because the chemical shifts of the corresponding resonances of *anti*-**1a** and *syn*-**1a** are distinctly different. Quantitative analysis of unseparated isomers was obtained by GC measurements.

Phenyl magnesium bromide was found to provide an excellent yield of **1a**. The aromatic Grignard reagents containing an electron-withdrawing group also gave the corresponding 1,3-diols in reasonable yield (entries 9, 10, 15, 16, and 17). However, the aromatic Grignard reagents bearing electron-donating substituents such as *p*-SMe and *p*-$SiMe_3$ afford the corresponding 1,3-diols in lower yield under the same conditions (entries 6 and 7). The reason for this is unclear and requires further study. The reaction (entry 11) gave the product in low yield because it is difficult to form a Grignard reagent from dibromobenzene. When the substituent of the Girgnared reagent was *p*-NMe_2, the 1,3-diol product was not detected. As the electronic donating capability of the substituent increases, the opportunity for the formation of a six-membered ring decreases.

The formation of 1,3-diols requires a break of a C−O bond and formation of a C−C bond in intermediate structures. In the addition stage, the intermediates originating from the first addition readily form a structure containing a four-membered ring due to the participation of a neighboring O atom.[12] It is unstable and tends to form a chelated compound containing a more stable six-membered ring based on an intramolecular mechanism.[13] The formation of the six-membered ring creates the conditions for the second stereoselective addition of a Grignard reagent, which results in the formation of the major *anti* isomer. Experiments containing a mixture of Grignard reagents provided further evidence for a stepwise addition procedure (see the Supporting Information).

Scheme 2 shows the possible mechanism. Initially, the arylmagnesium bromide and carbonyl group can form

Scheme 2. Possible Mechanism for the Reaction of Isopropenyl Acetate with Aryl Grignard Reagents



intermediate **A**, which would form intermediate **E** with a stable chair conformation through two transition states **B**, **D** and an intermediate **C**. **B** leads to the breaking of the C−O bond and formation of **C**. Intermediate **C** undergoes an intramolecular aldol reaction to give the chair intermediate **E** through transition state **D**. Also **C** can dissociate to intermediate **F** and acetophenone **2**, and further **2** reacts with a Grignard reagent to form product **3**. Entry 1(Table 2) was

(11) Aryl magnesium bromide Grignard reagents were used to react with vinyl acetate, and some corresponding diol products have been separated. Investigations of alkyl/vinyl Grignard reagents and BuLi reagent used in this reaction are in progress.

(12) Safont, V. S.; Moliner, V.; Oliva, M.; Castillo, R.; Andrés, J.; González, F.; Carda, M. *J. Org. Chem.* **1996**, *61*, 3467.

(13) (a) Wilson, K. W.; Roberts, J. D.; Young, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 2019. (b) Arnold, R. T.; Searles, S. *J. Am. Chem. Soc.* **1949**, *71*, 2021.

chosen as the model reaction. Our calculations[14] (Figure 2) on the potential intermediates starting from **A** suggest that

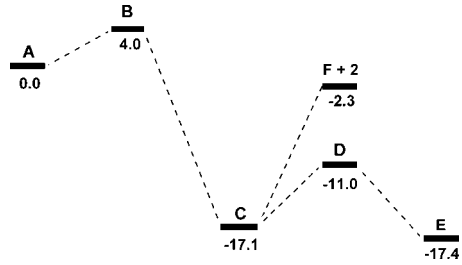
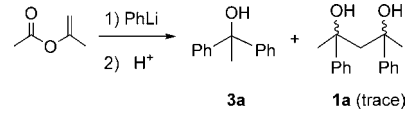


Figure 2. Calculations of the relative energy (kcal/mol) in the reaction of isopropenyl acetate with phenyl magnesium bromide Grignard reagent.

the stable chair conformation of the six-membered ring of **E** is 17.4 kcal/mol lower in energy than **A**, and that **F** is 2.3 kcal/mol lower in energy than **A**. It is expected that **E** is the main stable intermediate. After the formation of **E**, it further reacts with a Grignard reagent to give the final 1,3-diol products. Attack by path a leads to the major *anti* products of **1**, while path b leads to the minor *syn* products (Scheme 2). This means that the *anti* product is kinetically favored. Moreover, the calculation results also show that the *anti* isomer **1a** lies 1.2 kcal/mol lower in energy than *syn* isomer **1a**. Therefore, the *anti* product is favorably formed both kinetically and thermodynamically. The computed structures and intrinsic reaction coordinates (IRC) of the intermediate transition states are listed in the Supporting Information. The results of DFT calculations are in good agreement with those obtained experimentally (Table 2) and support the reaction mechanism shown in Scheme 2.[15]

The atomic radius of Li is smaller than that of Mg, and it has no vacant coordination site to form similar intermediates. So **3a** (88%) is formed when phenyl lithium reagents are reacted with isopropenyl acetate at low temperature (Scheme 3).[16]

Scheme 3. Reaction of Isopropenyl Acetate with PhLi under the Same Conditions As with PhMgBr



Acetylacetone (β-diketone) is produced by isomerization of isopropenyl acetate under heating (450−500 °C) in the presence or absence of catalyst.[17] From our results, it is obvious that this isomerization did not take place in the reaction of isopropenyl acetate with various Grignard reagents.

The addition of phenyl magnesium bromide to enol lactones derived from steroids formed β-hydroxy ketones by rearrangement not diols.[18] However, to the best of our knowledge, the application of the rearrangement of isopropenyl acetate with Grignard reagents has not been fully investigated from the synthetic point of view.

In conclusion, compared with other reported methods, this coupling of isopropenyl acetate with a Grignard reagent provides a simple and convenient process to symmetrical 1,3-diols. Additional or toxic reagents, such as transition metal salts, or organotin and related reagents are not required, and the reaction is carried out under readily accessible pressure and temperature. Further studies of the scope of the reaction are in progress.

Acknowledgment. This work was supported by the Nature Science Foundation of China (Nos. 20772028 and 21072053). We are grateful to Prof. Qing-Xiang Guo and Dr. Hai-Zhu Yu from the Department of Chemistry, University of Science & Technology of China for their helpful discussion.

Supporting Information Available: General methods, experimental procedures, spectroscopic data, ESI-HR MS of compounds, crystallographic data of **1a** in CIF format, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102520Y

(14) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. (b) Phenylmagnesium bromide and isopropenyl acetate were chosen as a chemical model. The DFT method was employed using the B3LYP hybrid functional and the 6-31G(d) basis set. Details are described in the Supporting Information.

(15) (a) Cui, X.; Li, Z.; Tao, C. Z.; Xu, Y.; Li, J.; Liu, L.; Guo, Q. X. *Org. Lett.* **2006**, *8*, 2467. (b) Jiang, B.; Cao, L. J.; Tu, S. J.; Zheng, W. R.; Yu, H. Z. *J. Comb. Chem.* **2009**, *11*, 612.

(16) Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715.

(17) (a) Hagemeyer, H. J.; Hull, D. C. *Ind. Eng. Chem.* **1949**, *41*, 2920. (b) Morita, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2006**, *71*, 6285.

(18) Zwahlen, K. D.; Horton, W. J.; Fujimoto, G. I. *J. Am. Chem. Soc.* **1957**, *79*, 3131.